

Amendments to the Specification:

Please replace paragraph [0028] beginning at page 8, line 27, with the following:

--[0028] FIG. 1 shows the sequences for the V_L chain of 2D12.5 (~~SEQ ID NO: 1~~) (SEQ ID NO:1) and the sequences for CDR1, CDR2, and CDR3 for the V_L chain of 2D12.5 (~~SEQ ID NOS: 2, 3, and 4, respectively~~) (SEQ ID NOS:2, 3, and 4, respectively). Figure 1 also shows the sequences for the V_H chain (SEQ ID NO:5) and the sequences for CDR1, CDR2, and CDR3 for the V_H chain of 2D12.5 (~~SEQ ID NOS: 6, 7, and 8, respectively~~) (SEQ ID NOS:6, 7, and 8, respectively).--

Please replace paragraph [0029] beginning at page 8, line 32, with the following:

--[0029] FIG. 2 shows the alignment of the amino acid sequence of the V_H chain of 2D12.5. In particular, Figure 2 shows the alignment of the native hybridoma sequence, the native cloned hybridoma sequence, the N87D sequence, the N87D_G53C sequence, the N87D_G54C sequence, and the N87D_G55C sequence (~~SEQ ID NOS: 9, 10, 11, 12, 13, and 14, respectively~~) (SEQ ID NOS:9, 10, 11, 12, 13, and 14, respectively). Note that the native hybridoma sequence shown corresponds to amino acids 2-119 of the V_H chain of 2D12.5 as set forth in SEQ ID NO:5. Therefore, N87D is N88D, G53C is G54C, G55C is G55C, and G55C is G56C if the Kabat standard numbering system is used to determine the positions of amino acid residues in an antibody heavy chain or light chain (*see, e.g., Kabat et al., Sequences of Proteins of Immunological Interest* 5th Ed., NIH Publication No. 91-3242 (1991)).--

Please replace paragraph [0030] beginning at page 9, line 9, with the following:

--[0030] **FIG. 3** shows the alignment of the nucleotide sequence of the V_H chain of 2D12.5. In particular, Figure 3 shows the alignment of the native hybridoma sequence, the native cloned hybridoma sequence, the N87D sequence, the N87D_G53C sequence, the N87D_G54C sequence, and the N87D_G55C sequence (~~SEQ ID NOS.: 15, 16, 17, 18, 19, and 20, respectively~~) SEQ ID NOS:15, 16, 17, 18, 19, and 20, respectively).--

Please replace paragraph [0031] beginning at page 9, line 14, with the following:

--[0031] **FIG. 4** shows the alignment of the amino acid sequence of the V_L chain of 2D12.5. In particular, Figure 4 shows the alignment of the native hybridoma sequence, the native cloned hybridoma sequence, and the N53C sequence (~~SEQ ID NOS.: 21, 22, and 23, respectively~~) SEQ ID NOS:21, 22, and 23, respectively). Note that the native hybridoma sequence shown corresponds to amino acids 2-110 of the V_L chain of 2D12.5 as set forth in SEQ ID NO:1. Therefore, N53C is N54C, if the Kabat standard numbering system is used.--

Please replace paragraph [0032] beginning at page 9, line 20, with the following:

--[0032] **FIG. 5** shows the alignment of the nucleotide sequence of the V_L chain of 2D12.5. In particular, Figure 5 shows the alignment of the native hybridoma sequence, the native cloned hybridoma sequence, and the N53C sequence (~~SEQ ID NOS.: 24, 25, and 26, respectively~~) SEQ ID NOS:24, 25, and 26, respectively).--

Please replace paragraph [0033] beginning at page 9, line 24, with the following:

--[0033] **FIG. 6** shows the alignment of the amino acid sequence of the chimeric V_L chain of 2D12.5 fused to the C_L kappa chain of a human anti-tetanus toxoid antibody. In particular,

Figure 6 shows the alignment of the native cloned hybridoma sequence fused to the C_L kappa chain, the N53C sequence fused to the C_L kappa chain, the native hybridoma sequence ~~fused to the C_L kappa chain~~, and the C_L kappa chain of the human anti-tetanus toxoid antibody template for gene assembly (~~SEQ ID NOS.: 27, 28, 29 and 30, respectively~~) SEQ ID NOS:27, 28, 29 and 30, respectively).--

Please replace paragraph [0034] beginning at page 9, line 30, with the following:

--[0034] **FIG. 7** shows the alignment of the nucleotide sequence of the chimeric V_L chain of 2D12.5 fused to the C_L kappa chain of a human anti-tetanus toxoid antibody. In particular, Figure 7 shows the alignment of the native cloned hybridoma sequence fused to the C_L kappa chain, the N53C sequence fused to the C_L kappa chain, the native hybridoma sequence ~~fused to the C_L kappa chain~~, and the C_L kappa chain of the human anti-tetanus toxoid antibody template for gene assembly (~~SEQ ID NOS.: 31, 32, 33, and 34, respectively~~) SEQ ID NOS:31, 32, 33, and 34, respectively).--

Please replace paragraph [0035] beginning at page 10, line 3, with the following:

--[0035] **FIG. 8** shows the alignment of the amino acid sequence of the chimeric V_H chain of 2D12.5 fused to the CH1 chain of a human anti-tetanus toxoid antibody. In particular, Figure 8 shows the alignment of the native cloned; hybridoma sequence fused to the CH1 chain, the N87D sequence fused to the CH1 chain, the N87D_G53C sequence fused to the CH1 chain, the N87D_G54C sequence fused to the CH1 chain, and the N87D_G55C sequence fused to the CH1 chain, the V_H chain of 2D12.5 fused to the CH1 chain expected sequence, and the native hybridoma sequence ~~fused to the CH1 chain~~, (~~SEQ ID NOS.: 35, 36, 37, 38, 39, 40, and 41, respectively~~) SEQ ID NOS:35, 36, 37, 38, 39, 40, and 41, respectively).--

Please replace paragraph [0036] beginning at page 10, line 10, with the following:

--[0036] **FIG. 9** shows the alignment of the nucleotide sequence of the chimeric V_H chain of 2D12.5 fused to the CH1 chain of a human anti-tetanus toxoid antibody. In particular, Figure 9 shows the alignment of the native cloned, hybridoma sequence fused to the CH1 chain, the N87D sequence fused to the CH1 chain, the N87D_G53C sequence fused to the CH1 chain, the N87D_G54C sequence fused to the V_H chain of 2D12.5 fused to the CH1 chain, and the N87D_G55C sequence fused to the CH1 chain, the CH1 chain expected sequence, and the native hybridoma sequence fused to the CH1 chain, (~~SEQ ID NOS.: 42, 43, 44, 45, 46, 47, and 48, respectively~~) SEQ ID NOS:42, 43, 44, 45, 46, 47, and 48, respectively).--

Please replace paragraph [0037] beginning at page 10, line 17, with the following:

--[0037] **FIG. 10** is a diagram depicting the strategy for assembly of the chimeric V_H chain of 2D12.5 fused to the CH1 chain of a human anti-tetanus toxoid antibody. FIG. 10A Primers = SEQ ID NOS:49-52. FIG. 10B Primers = SEQ ID NOS:49 and 52. FIG. 10D Mutation Methodology sequencess = SEQ ID NOS:53-56. FIG. 10D PCR Reaction Primers = SEQ ID NOS:57-63. --

Please replace paragraph [0038] beginning at page 10, line 19, with the following:

--[0038] **FIG. 11** is a diagram depicting the strategy for assembly of the chimeric V_L chain of 2D12.5 fused to the C_L kappa chain of a human anti-tetanus toxoid antibody. FIG. 11A Primers = SEQ ID NOS:64-67. FIG. 11B Primers = SEQ ID NOS:64 and 69. FIG. 11D Mutation Methodology sequencess = SEQ ID NOS:53, 54, 68 and 56. FIG. 11D PCR Reaction Primers = SEQ ID NOS:57, 69, 70, 71 and 63. FIG. 11F Primers = SEQ ID NOS:57, 65, 66 and 67.--

Please replace paragraph [0106] beginning at page 27, line 30, with the following:

--[0106] Peptide linkers, such as those used in the expression of recombinant single chain antibodies, may be employed as the linkers and connectors of the invention. Peptide linkers and their use are well known in the art. (*See, e.g.,* Huston *et al.*, 1988; Bird *et al.*, 1983; U.S. Patent No. 4,946,778; U.S. Patent No. 5,132,405; and Stemmer *et al.*, *Biotechniques* 14:256-265 (1993)). The linkers and connectors are flexible and their sequence can vary. Preferably, the linkers and connectors are long enough to span the distance between the amino acids to be joined without putting strain on the structure. For example, the linker ~~(gly₄ser)₃~~ (Gly₄Ser)₃ (SEQ ID NO:72) is a useful linker because it is flexible and without a preferred structure (Freund *et al.*, *Biochemistry* 33: 3296-3303 (1994)).--

Please replace paragraph [0108] beginning at page 28, line 11, with the following:

--[0108] The present invention provides for the expression of nucleic acids corresponding to the wild-type of essentially any antibody that can be raised against a metal chelate, and the modification of that antibody to include a reactive site. In a preferred embodiment, the Fab heavy chain of the wild-type antibody is the amino acid sequence set forth in ~~SEQ ID NO:5~~ SEQ ID NO:5 (FIG. 1) or is encoded by the nucleic acid sequence set forth in ~~SEQ ID NO:16~~ SEQ ID NO:16 (FIG. 3). In another preferred embodiment, the light-chain of the wild-type antibody is the amino acid sequence set forth in ~~SEQ ID NO:1~~ SEQ ID NO:1 (FIG. 1) or is encoded by the nucleic acid sequence set forth in ~~SEQ ID NO:25~~ SEQ ID NO:25 (FIG. 5). In yet another preferred embodiment, the invention provides a mutant of the light chain of 2D12.5 in which N-53 is substituted by C and that has the amino acid sequence set forth in ~~SEQ ID NO:23~~ SEQ ID NO:23 (FIG. 4), or is encoded by the nucleic acid sequence set forth in ~~SEQ ID NO:26~~ SEQ ID NO:26 (FIG. 5). In yet another preferred embodiment, the invention provides a mutant of the heavy-chain of 2D12.5 in which N-87 is replaced by D and that has the amino acid sequence set forth in ~~SEQ ID NO:11~~ SEQ ID NO:11 (FIG. 2) or is encoded by the nucleic acid

sequence set forth in ~~SEQ ID NO: 17~~ SEQ ID NO:17 (FIG. 3). In yet another preferred embodiment, the invention provides a mutant of the heavy-chain of 2D12.5 in which N-87 is replaced by D and G-53 is replaced by C, and that has the amino acid sequence set forth in ~~SEQ ID NO: 12~~ SEQ ID NO:12 (FIG. 2) or is encoded by the nucleic acid sequence set forth in ~~SEQ ID NO: 18~~ SEQ ID NO:18 (FIG. 3). In yet another preferred embodiment, the invention provides a mutant of the heavy-chain of 2D12.5 in which N-87 is replaced by D and G-54 is replaced by C, and that has the amino acid sequence set forth in ~~SEQ ID NO: 13~~ SEQ ID NO:13 (FIG. 2) or is encoded by the nucleic acid sequence set forth in ~~SEQ ID NO: 19~~ SEQ ID NO:19 (FIG. 3). In yet another preferred embodiment, the invention provides a mutant of the heavy-chain of 2D12.5 in which N-87 is replaced by D and G-55 is replaced by C, and that has the amino acid sequence set forth in ~~SEQ ID NO: 14~~ SEQ ID NO:14 (FIG. 2) or is encoded by the nucleic acid sequence set forth in ~~SEQ ID NO: 20~~ SEQ ID NO:20 (FIG. 3).--

Please replace paragraph [0235] beginning at page 56, line 32, with the following:

--[0235] In a preferred form, the antibodies are recombinantly produced as fusion proteins with a second, antitumor antibody that acts to target the fusion protein to an antigen of a targeted tumor. Dozens of antitumor antigens and antibodies against them are known in the art, many of which are in clinical trials. Examples include AMD-Fab, LDP-02, aCD-11a, aCD-18, a-VEGF, a-IgE, and Herceptin, from Genentech, ABX-CBL, ABX-EGF, and ABX-IL8, from Abgenix, and aCD3, Smart 195 and Zenepax from Protein Design Labs. In preferred forms, the antibody is HMFG1, L6, or Lym-1, with Lym-1 being the most preferred. In preferred embodiments, an scFv or dsFv form of the antibody is employed. Formation of scFvs and dsFvs is known in the art. Formation of a scFv of Lym-1, for example, is taught Bin Song *et al.*, *Biotechnol Appl Biochem* 28(2):163-7 (1998). See, also *Cancer Immunol. Immunother.* 43: 26-30 (1996). The two antibodies can be linked directly or, more commonly, are connected by a short peptide linker, such as Gly₄Ser repeated 3 times (SEQ ID NO:72).--

Appl. No. 10/631,258

PATENT

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Reply to Notice to File Missing Parts of November 7, 2003

Please insert the accompanying paper copy of the Sequence Listing, page numbers 1 to 31, at the end of the application.